Amish lethal microcephaly

Amish lethal microcephaly is a disorder in which infants are born with a very small head and underdeveloped brain.

Infants with Amish lethal microcephaly have a sloping forehead and an extremely small head size. They may also have an unusually small lower jaw and chin (micrognathia) and an enlarged liver (hepatomegaly).

Affected infants may have seizures and difficulty maintaining their body temperature. Often they become very irritable starting in the second or third month of life. A compound called alpha-ketoglutaric acid can be detected in their urine (alpha-ketoglutaric aciduria), and during episodes of viral illness they tend to develop elevated levels of acid in the blood and tissues (metabolic acidosis). Infants with this disorder typically feed adequately but do not develop skills such as purposeful movement or the ability to track faces and sounds. Affected infants live only about six months.

Frequency

Amish lethal microcephaly occurs in approximately 1 in 500 newborns in the Old Order Amish population of Pennsylvania. It has not been found outside this population.

Genetic Changes

Mutations in the *SLC25A19* gene cause Amish lethal microcephaly.

The *SLC25A19* gene provides instructions for producing a protein that is a member of the solute carrier (SLC) family of proteins. Proteins in the SLC family transport various compounds across the membranes surrounding the cell and its component parts. The protein produced from the *SLC25A19* gene transports a molecule called thiamine pyrophosphate into the mitochondria, the energy-producing centers of cells. This compound is involved in the activity of a group of mitochondrial enzymes called the dehydrogenase complexes, one of which is the alpha-ketoglutarate dehydrogenase complex. The transport of thiamine pyrophosphate into the mitochondria is believed to be important in brain development.

All known individuals with Amish lethal microcephaly have a mutation in which the protein building block (amino acid) alanine is substituted for the amino acid glycine at position 177 of the SLC25A19 protein, written as Gly177Ala or G177A. Researchers believe that this mutation interferes with the transport of thiamine pyrophosphate into the mitochondria and the activity of the alpha-ketoglutarate dehydrogenase complex, resulting in the abnormal brain development and alpha-ketoglutaric aciduria seen in Amish lethal microcephaly.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- Amish microcephaly
- MCPHA
- microcephaly, Amish type

Diagnosis & Management

These resources address the diagnosis or management of Amish lethal microcephaly:

- GeneReview: Amish Lethal Microcephaly
  https://www.ncbi.nlm.nih.gov/books/NBK1365
- Genetic Testing Registry: Amish lethal microcephaly
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1846648/
- MedlinePlus Encyclopedia: Microcephaly
  https://medlineplus.gov/ency/article/003272.htm

These resources from MedlinePlus offer information about the diagnosis and management of various health conditions:

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Microcephaly
  https://medlineplus.gov/ency/article/003272.htm
- Health Topic: Brain Malformations
  https://medlineplus.gov/brainmalformations.html

Genetic and Rare Diseases Information Center

- Amish lethal microcephaly
  https://rarediseases.info.nih.gov/diseases/8606/amish-lethal-microcephaly

Additional NIH Resources

- NINDS Fact Sheet: Microcephaly
  https://www.ninds.nih.gov/Disorders/All-Disorders/Microcephaly-Information-Page

Educational Resources

- Amish, Mennonite and Hutterite Genetic Disorder Database
  http://www.biochemgenetics.ca/plainpeople/singleview.php?id=2360
- Disease InfoSearch: Amish Lethal Microcephaly
  http://www.diseaseinfosearch.org/Amish+Lethal+Microcephaly/376
- Lucille Packard Children's Hospital: Microcephaly
  http://www.stanfordchildrens.org/en/topic/default?id=microcephaly-90-P02610
- MalaCards: microcephaly, amish type
  http://www.malacards.org/card/microcephaly_amish_type
- Orphanet: Amish lethal microcephaly
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99742

Patient Support and Advocacy Resources

- Birth Defect Research for Children
  http://www.birthdefects.org/
- March of Dimes Foundation
  http://www.marchofdimes.org/

GeneReviews

- Amish Lethal Microcephaly
  https://www.ncbi.nlm.nih.gov/books/NBK1365

Genetic Testing Registry

- Amish lethal microcephaly
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1846648/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Microcephaly%5BMAJR%5D%29+AND+%28%28Amish%5BALL%5D%29+OR+%28mcpha%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- MICROCEPHALY, AMISH TYPE
  http://omim.org/entry/607196

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Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/amish-lethal-microcephaly

Reviewed: July 2013
Published: February 14, 2017

Lister Hill National Center for Biomedical Communications
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National Institutes of Health
Department of Health & Human Services